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New antimicrobial agents for the treatment of Gram-positive bacterial infections

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ABSTRACT

Since the 1970s, resistance to antimicrobial agents has become an escalating problem. In the last 25 years, treatment of infections caused by Gram-positive bacteria has been more problematical than ever, with infections being caused by multidrug-resistant organisms, particularly methicillin-resistant staphylococci, penicillin- and erythromycin-resistant pneumococci, and vancomycin-resistant enterococci. There is a continuing effort in the pharmaceutical industry to develop new antimicrobial agents for the treatment of resistant infections. Linezolid, quinupristin–dalfopristin, daptomycin, tigecyline, new glycopeptides and ceftobiprole are the main agents recently introduced or under clinical development. This review summarises their major properties, the results of recent studies with these agents, and future treatment possibilities.

Keywords Ceftobiprole, daptomycin, linezolid, quinupristin–dalfopristin, review, tigecycline

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INTRODUCTION

The introduction of benzylpenicillin in the 1940s ushered in an era of effective treatment of bacterial infections, but it soon became apparent that some strains of *Staphylococcus aureus* were drug-resistant because of the production of β-lactamase. Since the mid-1970s, resistance to antimicrobial agents has become an escalating problem [1]. A striking change during the past quarter-century has been the increasing importance of infections caused by Gram-positive bacteria, which might have resulted from the previous emphasis placed on controlling Gram-negative bacterial infections. Today, it is necessary to deal with infections caused by multidrug-resistant organisms, particularly methicillin-resistant staphylococci, penicillin- and erythromycin-resistant pneumococci, and vancomycin-resistant enterococci (VRE). The emergence and rapid spread of strains of methicillin-resistant *Staph. aureus* (MRSA), which are resistant not only to all β-lactams, but also to the other main antibiotic classes, has resulted in an increased use of glycopeptide antibiotics, i.e., vancomycin and teicoplanin. Unfortunately, VRE were detected in 1986, both in France and the UK, and multidrug-resistant strains of enterococci are now encountered throughout Europe and the USA [2–4]. Within 1 year of their initial detection, resistant strains were associated with infections in the USA, and they accounted for 26% of isolates of enterococci from blood in the USA by the year 2000. Since 1996, vancomycin-intermediate *Staph. aureus* (VISA) isolates with a vancomycin MIC of 8–16 mg/L have been reported, and this has been followed since 2002 by reports of vancomycin-resistant *Staph. aureus* (MIC ≥32 mg/L) [5–8].

As a result of these developments, there is an urgent need for effective new antimicrobial agents, as well as for prudent use of existing agents. Linezolid, quinupristin–dalfopristin, daptomycin, tigecyline, new glycopeptides and ceftobiprole are the main new agents that have recently become available for use or are under clinical development. This review summarises their properties, the results of recent studies with these agents, and future treatment possibilities.

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LINEZOLID

Linezolid (Zyvox®) is the first of a new class of antimicrobial agents, the oxazolidinones. Linezolid is a synthetic antibiotic that, depending on the organism and the linezolid concentration, has a bacteriostatic or bactericidal effect by inhibiting protein synthesis at the ribosomal level and by preventing the formation of the protein initiation complex [9]. Linezolid is active against most Gram-positive bacteria, including methicillin-sensitive *Staph. aureus* (MSSA) and MRSA, *Streptococcus pneumoniae* (including multidrug-resistant strains), *Streptococcus pyogenes* and *Streptococcus agalactiae*. Rare occurrences of linezolid resistance among VRE in North America (0.8–1.8%), caused by a G2576U ribosomal mutation, have been reported, and an intrinsic resistance gene rendering a clinical strain of MRSA resistant to linezolid has been described [10–13]. Although resistant strains of *Staph. aureus* have been reported, linezolid remains highly active against MRSA (MIC_{90} 2 mg/L) [12–15].

Linezolid was approved by the US Food and Drug Administration (FDA) in 2000 for the treatment of uncomplicated and complicated skin and soft-tissue infections, including diabetic foot infections without concomitant osteomyelitis, community-acquired and nosocomial pneumonia, and vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteraemia [9]. Activity against *Nocardia* spp. and *Mycobacterium* spp. has also been demonstrated, including cases of central nervous system infection and infective endocarditis [14–18].

The high bioavailability of linezolid, whether administered orally or intravenously, with a standard twice-daily dose of 600 mg, makes it a suitable alternative for the treatment of infections that require the prolonged use of antimicrobial agents [19,20]. Tissue penetration is good, with marked accumulation in sweat, saliva and epithelial lining. Linezolid is reported to be equally effective or even superior to vancomycin for the treatment of pneumonia and soft-tissue infections [21–23]. However, recent meta-analyses have suggested that linezolid's apparent superiority for the treatment of pneumonia and bone and joint infections has limitations. Cases of MRSA endocarditis that failed to respond to linezolid treatment have also been reported [15,24,25].

Linezolid is generally well-tolerated, with the most common adverse effects being diarrhoea, headache and nausea. Like many other antibiotics, it may predispose to pseudo-membranous colitis following the overgrowth of *Clostridium difficile* [26]. Myelosuppression (including anaemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients taking linezolid. In cases with a known treatment outcome, the affected haematological parameters rose to pre-treatment levels when linezolid was discontinued. Complete blood counts should be monitored weekly in patients taking linezolid, and particularly in patients who are prescribed linezolid for >2 weeks, patients with pre-existing myelosuppression, patients receiving concomitant drugs that produce bone marrow suppression, and patients with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of linezolid therapy should be considered for patients who develop, or have worsening, myelosuppression. Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including such anti-depressants as selective serotonin re-uptake inhibitors, have been reported. Linezolid has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome or untreated hyper-thyroidism [27].

Lactic acidosis, peripheral neuropathy and optic neuropathy are other adverse effects of linezolid treatment. A recent study that compared linezolid to vancomycin, oxacillin and dicloxacillin (comparator antibiotics) for the treatment of seriously-ill patients with intravascular catheter-related bloodstream infections, including patients with catheter-site infections, reported a higher mortality rate in the linezolid arm. There was no difference in the mortality rate of patients with Gram-positive infections who were treated with other antibiotics. Furthermore, the mortality rate was higher only for patients who were infected only with Gram-negative organisms, or who were infected with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study and were treated with linezolid. Therefore, if infection with Gram-negative bacteria is known or suspected, appropriate therapy should be started immediately (http://www.fda.gov/cder/drug/InfoSheets/HCP/linezolidHCP.htm).

Linezolid is an effective alternative antimicrobial agent for the treatment of Gram-positive infections, but because of the absence of placebo-controlled double-blind studies, linezolid should be used with extreme caution in patients with vancomycin-induced nephrotoxicity or a documented absence of response to vancomycin.

QUINUPRISTIN–DALFOPRISTIN

Quinupristin–dalfopristin (Synercid®) is a fixed mixture (30:70) of semi-synthetic streptogramin derivatives. These compounds enter bacterial cells by diffusion and bind to different sites on the 50S ribosomal subunit, resulting in an irreversible inhibition of bacterial protein synthesis [28]. Dalfopristin blocks the reaction catalysed by the peptidyl transferase catalytic centre of the 50S ribosome by inhibiting substrate attachment to the P-site and A-site of the ribosome. Quinupristin inhibits peptide chain elongation. The synergic effect of this drug combination appears to result from the fact that it targets both early and late stages of protein synthesis [29]. Thus, quinupristin–dalfopristin is bacteriostatic against *E. faecium* and bactericidal against MSSA, MRSA and *Strep. pyogenes*. It is ineffective against *Enterococcus faecalis*. In the USA, the only FDA-approved use of quinupristin–dalfopristin as an anti-staphylococcal agent is for the treatment of adults with complicated skin and skin-structure infections caused by MSSA. Otherwise, the drug is approved for complicated skin and skin-structure infections caused by *Strep. pyogenes*, and for serious VRE infections associated with bacteraemia [30]. Resistance in *E. faecium* was reported by the SENTRY antimicrobial surveillance programme in Europe and North America to be 10.0% and 0.6%, respectively [10].

The results of studies in which the effectiveness of quinupristin–dalfopristin for the treatment of skin and soft-tissue infections was compared to that of other agents have generally been satisfactory, despite the fact that quinupristin–dalfopristin is inferior to other agents for the treatment of pneumonia and infective endocarditis [24,31].

Quinupristin–dalfopristin can only be administered by the intravenous route in a dextrose 5% w/v solution. Drug elimination is through bile into faeces, but clearance may be slightly impaired in patients with renal insufficiency. The drug has significant toxicity problems, including arthralgia–myalgia syndrome and venous intolerance. Pain and inflammation at the infusion site is experienced by up to 74% of patients [31–33]. Hyper-bilirubinaemia and liver toxicity can also occur. Quinupristin–dalfopristin has been shown to be a major inhibitor of the activity of the cytochrome P450 3A4 isoenzyme, and drug interactions (especially with cyclosporine) should be monitored carefully during therapy. Although the drug itself does not induce QTc prolongation, it can interfere with the metabolism of other drug products that are associated with QTc prolongation [33,34].

Quinupristin–dalfopristin is the first parenteral streptogramin and offers a unique alternative treatment for infections caused by multidrug-resistant Gram-positive bacteria, but the broad spectrum of adverse effects makes it an inferior choice to other agents.

DAPTOMYCIN

Daptomycin (Cubicin®) is the first of a new class of cyclic lipopeptides. This agent is derived from the fermentation of a strain of *Streptomyces roseosporus*. Originally developed during the early 1980s, daptomycin was initially shelved because of concerns about skeletal-muscle toxicity. This effect was not seen with lower doses, and daptomycin received approval by the FDA in September 2003 for the treatment of complicated skin and soft-tissue infections.

Daptomycin attaches to the cytoplasmic membrane of Gram-positive bacteria, forming a channel that allows the efflux of potassium, causing depolarisation of the membrane, along with dysfunction of macromolecular synthesis and collapse of the organism without lysis. This mechanism of action is concentration-dependent, free calcium ion-dependent, rapid and unique [35]. Some other bactericidal antibiotics, most notably β-lactams, cause bacterial cells to lyse. This is potentially harmful, as it may release bacterial endotoxins and other inflammatory cell components into the circulation, triggering cytokine cascades, and potentially leading to septic shock and multiple organ failure [36]. The antimicrobial effect of daptomycin is concentration-dependent, with the optimal dose for serious bloodstream and endovascular infections reported to be 6 mg/kg once-daily. The recommended dose for skin and skin-structure infections is 4 mg/kg once-daily.

Daptomycin also has a post-antibiotic effect lasting 1.5–6 h [37].

Although daptomycin is approved by the FDA for the treatment of complicated skin and skin-structure infections that involve MRSA and other Gram-positive bacteria, its rapid bactericidal effect makes it appropriate for the treatment of other kinds of infection. The bactericidal activity of daptomycin, vancomycin, linezolid and quinupristin–dalfopristin against MRSA and VISA has been compared using in-vitro time-kill studies [38]. Against all organisms tested, daptomycin had bactericidal activity equal to or greater than that of the other agents [39].

Daptomycin has efficacy comparable to standard therapy for the treatment of skin and skin-structure infections. It has been used successfully to treat bone and joint infections [40,41]. Successful results have also been reported for the treatment of bacteraemia and right-sided infective endocarditis, but not for the treatment of community-acquired pneumonia. When daptomycin was compared with standard therapy for bacteraemia and endocarditis caused by *Staph. aureus*, a successful outcome was documented in 53 of 120 of patients who received daptomycin, compared with 48 of 115 patients who received standard therapy (44.2% vs. 41.7%, respectively; absolute difference, 2.4%; 95% CI 10.2–15.1) [42–44]. The lack of efficacy of daptomycin in treating community-acquired pneumonia is thought to be a consequence of a reduction of daptomycin activity in the presence of lung surfactant [45].

Resistance to daptomycin is rare. Spontaneous resistance is uncommon, emerging *in vitro* at a rate of $<1 \times 10^{-10}$, but resistance can be induced by serial passage in increasing concentrations of the antibiotic [46]. There have been several reports of daptomycin resistance emerging in clinical isolates of MRSA from patients who received prolonged treatment [47,48]. The once-daily dosing schedule and the favourable safety profile (except for some concerns regarding rhabdomyolysis and neuropathy) make daptomycin an attractive option for the treatment of Gram-positive infections [44].

TIGECYCLINE

Tigecycline (Tygacil®) is a new, semi-synthetic glycylcycline, which is a new class of antimicrobial agent. Glycocides are derivatives of tetracyclines, and have broad-spectrum activity against susceptible and multidrug-resistant strains of bacteria. Tigecycline, the first glycylcycline, demonstrates potent in-vitro activity against a wide range of Gram-positive and Gram-negative bacteria, including MRSA and tetracycline-resistant *Staph. aureus*, as well as many multidrug-resistant Gram-negative pathogens and anaerobes [49]. The potent in-vitro activity of tigecycline resulted in its approval by the FDA for the treatment of skin, soft-tissue and intra-abdominal infections [50].

Like tetracycline, tigecycline exerts its mechanism of action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation in bacteria. This blockade prevents the entry of aminoacyl tRNA molecules into the A-site of the ribosome, resulting in the loss of peptide formation [51,52]. Tigecycline is highly effective *in vivo* against most Gram-positive organisms, including *Staph. aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Strep. pneumoniae*, and group A, group B and viridans streptococci. It also has good in-vitro activity against most Gram-negative organisms and anaerobes. Interestingly, some atypical microorganisms, e.g., *Mycobacterium abscessus*, *Mycobacterium chelonae*, the *Mycobacterium fortuitum* group, *Mycobacterium marinum*, *Chlamydia pneumoniae*, *Mycoplasma hominis*, *Mycoplasma pneumonia* and *Ureaplasma urealyticum*, are also susceptible to tigecycline [53]. Tigecycline has demonstrated excellent overall tissue penetration in animal studies, including bone, bone marrow, salivary gland, thyroid, spleen, kidney and cerebrospinal fluid [53].

Phase 3 randomised double-blind studies have confirmed the efficacy of tigecycline for the treatment of skin and skin-structure infections, and for intra-abdominal infections. Sacchidanand *et al.* [54] reported that tigecycline was not inferior to a combination of aztreonam and vancomycin for the treatment of complicated skin and skin-structure infections. Cure rates and microbiological eradication rates were similar for tigecycline and a comparator group of antibiotics, at 82.9% and 82.3%, respectively [54]. In two other phase 3 double-blind studies involving 833 clinically evaluable patients (422 treated with tigecycline and 411 treated with vancomycin and aztreonam), clinical response rates were similar for tigecycline (86.5%) (95% CI 82.9–89.6%) and vancomycin–aztreonam (88.6%) (95% CI 85.1–91.5%) [55].

In a pooled analysis of two phase 3 double-blind trials designed to evaluate the safety and efficacy of tigecycline in comparison with that of imipenem–cilastatin, clinical cure rates for the microbiologically evaluable group among 1642 adults with complicated intra-abdominal infections were 86.1% for tigecycline and 86.2% for imipenem–cilastatin (95% CI for the difference −4.5 to 4.4%; p <0.0001 for non-inferiority) [56]. Similar results were obtained in another study which demonstrated that tigecycline was not inferior for treating complicated intra-abdominal infections [57].

Clinically significant organ toxicity has not been observed in association with tigecycline use during clinical trials. Nausea and vomiting are the most common side-effects, and these are dose-limited and are not diminished by reducing the rate of drug infusion [58]. The low potential of the drug for the development of resistance, which is almost a rule for other tetracyclines, combined with its broad-spectrum activity against multidrug-resistant pathogens, provides key advantages. Therefore, tigecycline presents a genuinely new therapeutic option for the treatment of infections caused by multidrug-resistant bacteria.

NEW GLYCOPEPTIDES

Oritavancin, telavancin and dalbavancin are new glycopeptides currently in clinical development, and appear to be potent molecules with favourable pharmacokinetic and pharmacodynamic properties.

Oritavancin

This agent was obtained by reductive alkylation with 4′-chloro-biphenylcarboxaldehyde of chloroeremomycin, which differs from vancomycin by the addition of a 4-epi-vancosamine sugar, and the replacement of vancosamine of the disaccharide moiety by an epivancosamine [59]. Although oritavancin has a general spectrum of activity comparable to that of vancomycin, it offers considerable advantages in terms of intrinsic activity (especially against streptococci). Unlike vancomycin, oritavancin can dimerise, leading to a cooperative interaction with two stems of the growing peptidoglycan chain. The lipophilic side-chain assists in membrane-anchoring by hydrophobic interactions, stabilising the dimer in the most favourable position. Evidence also exists for another mechanism of action of oritavancin, namely inhibition of the transglycosylation step of cell-wall synthesis [60,61].

Oritavancin is active against most isolates of streptococci and staphylococci, as well as *Peptostreptococcus* spp., *Propionibacterium acnes*, *Clostridium perfringens* and *Corynebacterium jeikeium*. Its activity against enterococci is not affected by the presence of *vanA*-, *vanB*- and *vanC*-encoded vancomycin resistance, or by aminoglycoside resistance. Its activity against pneumococci and viridans streptococci is not affected by the presence of intermediate- or high-level penicillin resistance. In addition, the presence of methicillin resistance does not affect the activity of oritavancin against *Staph. aureus* or coagulase-negative staphylococci. Oritavancin is inactive against Gram-negative aerobes and anaerobes [62].

Oritavancin is active in a number of animal models of infection, including a central venous catheter-associated infection model in rats (vancomycin-resistant *E. faecalis*), a rabbit endocarditis model (MRSA, vancomycin-sensitive and vancomycin-resistant *E. faecalis*), a neutropenic mouse thigh model (*Staph. aureus* ATCC 13709), and a rabbit meningitis model (penicillin-sensitive *Strep. pneumoniae*) [63–68].

In a phase 2 clinical trial involving complicated skin and skin-structure infections, oritavancin was not inferior to vancomycin and cephalexin, but had a shorter mean duration of activity [69]. In a phase 2 open-label randomised trial comparing oritavancin (5–10 mg/kg once-daily for 10–14 days) with vancomycin (15 mg/kg twice-daily) and a β-lactam for 10–14 days in patients with *Staph. aureus*-associated bacteraemia, oritavancin was as effective as the comparators, with higher clinical and bacteriological success in the cohort receiving 10 mg/kg, and with no evidence of increased side-effects [70]. The exceptionally long terminal half-life suggests the existence of storage sites within the organism. Studies using cultured macrophages indicate that the drug accumulates slowly (by an endocytic process), but importantly, in the lysosomes, from which efflux is extremely slow [71]. The clinical importance of this property is currently unknown.

Telavancin

Telavancin (TD-6424) is a semi-synthetic derivative of vancomycin, possessing a hydrophobic side-chain on the vancosamine sugar (decylaminoethyl) and a (phosphonomethyl) aminoethyl substituent on the cyclic peptidic core [72]. Pharmacological studies suggest that the enhanced activity of telavancin against *Strep. pneumoniae*, *Staph. aureus* (to a lesser extent) and staphylococci and enterococci harbouring the *vanA* gene cluster results from a complex mechanism of action, which, on the basis of data obtained with close analogues, involves a perturbation of lipid synthesis and possible membrane disruption [73].

Telavancin is active *in vitro* against all Gram-positive pathogens, including *vanA*-positive enterococci. As with oritavancin, extreme potency is observed for streptococci, particularly *Strep. pneumoniae* [74]. Telavancin is active in an in-vitro biofilm model, whereas vancomycin and a number of other antibiotics were much less effective [75]. Telavancin is highly effective in animal models of relevant infections [76–78], and tissue penetration of telavancin is high after intravenous administration in healthy subjects [79]. Telavancin has proven to be effective and safe for patients with skin and soft-tissue infections, with cure rates of up to 96%, compared with 90% for standard therapy. Concerns related to QTc elevation will be clarified following further studies [80,81].

Dalbavancin

This agent is a semi-synthetic derivative of the teicoplanin-related glycopeptide A40925, modified with an amide appendage at the C-terminus and an alteration of the hydrophobic acylglucosamine substituent. Like teicoplanin, dalbavancin is active against *vanB*-positive enterococci, as well as staphylococci and other important species [73]. The pharmacokinetic profile of dalbavancin is characterised by a long half-life of *c.* 7 days. This allows a once-weekly regimen for the treatment of infections caused by Gram-positive bacteria. This weekly regimen may offer certain advantages, e.g., improved patient compliance and reduced use of resources compared with antimicrobial agents administered more frequently [82]. Dalbavancin has been shown to be as effective as linezolid twice-daily for the treatment of complicated skin and skin-structure infections [83], and is more effective than most anti-Gram-positive agents, both *in vitro* and *in vivo* [84,85].

In addition to complicated skin and skin-structure infections, dalbavancin has been used to treat catheter-related bloodstream infection. In a randomised controlled open-label multicentre phase 2 trial that involved 75 adult patients with catheter-related bloodstream infection, the results were overwhelmingly in favour of dalbavancin, albeit with limitations [86]. To date, adverse events have been mild and limited, with the most common being pyrexia, headache, nausea, oral candidiasis, diarrhoea and constipation. Consequently, dalbavancin appears to be a promising antimicrobial agent for the treatment of infections caused by Gram-positive bacteria.

CEFTOBIPROLE

Ceftobiprole is a novel broad-spectrum β-lactamase-stable parenteral cephalosporin with strong affinity for the penicillin-binding proteins PBP2a and PBP2x, responsible for resistance in staphylococci and pneumococci, respectively. Ceftobiprole can also bind to relevant penicillin-binding proteins of resistant Gram-positive and Gram-negative bacteria, and appears to have a low ability to select for resistance [87,88]. In-vivo screening models suggest good activity of ceftobiprole against Gram-positive and Gram-negative bacteria. Several animal models have been used in the evaluation of ceftobiprole, including mouse sepsis, abscess and pneumonia models, rat endocarditis and tissue cage models, and a rabbit endocarditis model [89,90]. These models suggest that ceftobiprole should have clinical efficacy as an empirical treatment for severe clinical infections.

Several phase 3 studies of ceftobiprole for the treatment of complicated skin and skin-structure infections have been performed. One study compared intravenous ceftobiprole (500 mg every 12 h) with intravenous vancomycin (1 g every 12 h) in patients with complicated skin and skin-structure infections caused by Gram-positive bacteria. Staphylococci were the predominant pathogens, and >25% of the microbiologically evaluable patients had infections caused by MRSA. In the clinically evaluable population, efficacy and adverse events were comparable between treatment arms. Additional clinical trials involving

complicated skin and skin-structure infections and pneumonia patients are underway to evaluate ceftobiprole as a treatment for infections caused by both Gram-positive and Gram-negative bacteria. The broad-spectrum activity of ceftobiprole may allow it to be used as monotherapy for serious nosocomial infections for which combination therapy would otherwise be required [91,92].

CONCLUSIONS

Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline, new glycopeptides and ceftobiprole are the most important novel agents that are currently being considered as alternatives for the treatment of infections caused by Gram-positive bacteria. Doripenem, iclaprim (a recent example of a novel diamonipyrimidine), ranbezolide (a novel oxazolidinone) and ceftaroline (a novel cephalosporin with impressive anti-MRSA and anti-pneumococcal activity) are other agents that are currently under investigation [93–96].

Changing patterns of resistance have compounded and exacerbated the need for new antimicrobial agents. Each of the above compounds has its own unique advantages and disadvantages, so each agent should be used cautiously when conventional treatment fails. The appropriate indications and cost-effectiveness of these molecules will determine future treatment options. Until then, prudent use of existing antibiotics, with strict reinforcement of infection control precautions, should continue to be the rule in the treatment of Gram-positive infections.

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